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Combined oral contraceptives: venous thrombosis (Review)

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[Intervention Review]

Combined oral contraceptives: venous thrombosis

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ABSTRACT

Background

Combined oral contraceptive (COC) use has been associated with venous thrombosis (VT) (i.e., deep venous thrombosis and pulmonary embolism). The VT risk has been evaluated for many estrogen doses and progestagen types contained in COC but no comprehensive comparison involving commonly used COC is available.

Objectives

To provide a comprehensive overview of the risk of venous thrombosis in women using different combined oral contraceptives.

Search methods

Electronic databases (Pubmed, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and ScienceDirect) were searched in 22 April 2013 for eligible studies, without language restrictions.

Selection criteria

We selected studies including healthy women taking COC with VT as outcome.

Data collection and analysis

The primary outcome of interest was a fatal or non-fatal first event of venous thrombosis with the main focus on deep venous thrombosis or pulmonary embolism. Publications with at least 10 events in total were eligible. The network meta-analysis was performed using an extension of frequentist random effects models for mixed multiple treatment comparisons. Unadjusted relative risks with 95% confidence intervals were reported. Two independent reviewers extracted data from selected studies.

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Main results

3110 publications were retrieved through a search strategy; 25 publications reporting on 26 studies were included. Incidence of venous thrombosis in non-users from two included cohorts was 0.19 and 0.37 per 1 000 person years, in line with previously reported incidences of 0.16 per 1 000 person years. Use of combined oral contraceptives increased the risk of venous thrombosis compared with non-use (relative risk 3.5, 95% confidence interval 2.9 to 4.3). The relative risk of venous thrombosis for combined oral contraceptives with 30-35 µg ethinylestradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone were similar and about 50-80% higher than for combined oral contraceptives with levonorgestrel. A dose related effect of ethinylestradiol was observed for gestodene, desogestrel, and levonorgestrel, with higher doses being associated with higher thrombosis risk.

Authors' conclusions

All combined oral contraceptives investigated in this analysis were associated with an increased risk of venous thrombosis. The effect size depended both on the progestogen used and the dose of ethinylestradiol. Risk of venous thrombosis for combined oral contraceptives with 30-35 µg ethinylestradiol and gestodene, desogestrel, cyproterone acetate and drospirenone were similar, and about 50-80% higher than with levonorgestrel. The combined oral contraceptive with the lowest possible dose of ethinylestradiol and good compliance should be prescribed—that is, 30 µg ethinylestradiol with levonorgestrel.

PLAIN LANGUAGE SUMMARY

Contraceptive pills and venous thrombosis

Contraceptive pills are among the most popular contraception methods worldwide. A combined oral contraceptive pill contains two components, the estrogen and the progestagen compound. Despite its reliable contraception action, these pills may present side-effects including obstruction of leg and pulmonary vessels by clots (venous thrombosis). This side-effect is rare but the most frequently occurring serious adverse effect. Different combination pills show different vessel clotting obstruction tendencies (venous thrombosis risk). Evaluation of these different tendencies may play an important role in choosing the safest pill when starting pill use. COC containing higher estrogen doses (>30 µg) with levonorgestrel (a progestagen) or containing cyproterone acetate or drospirenone as progestagen are associated with higher VT risk than the oral contraceptive pill with 30 µg estrogen and levonorgestrel as progestagen. All combined monophasic oral contraceptive pills have the same effectiveness, that is preventing unwanted pregnancies.

BACKGROUND

Description of the condition

Venous thrombosis comprises deep-vein thrombosis (DVT) and pulmonary embolism. DVT typically starts in the calf veins, from where it may extend to the proximal veins and subsequently cause pulmonary embolism (Kearon 2003). Approximately one-third of patients with symptomatic venous thrombosis manifest pulmonary embolism (White 2003; Huerta 2007). Venous thrombosis is associated with genetic (i.e., carriers of thrombophilic disorders and a positive family history for venous thrombosis) and acquired risk factors (i.e., surgery, trauma, marked immobility, pregnancy, hormonal replacement therapy, previous venous thrombotic event, active cancer). In women of reproductive age, an important risk factor is oral contraceptive use. Oral contraceptives

and inherited thrombophilic defects (i.e., factor V Leiden mutation, deficiency of protein C, protein S or antithrombin, high levels of factor VIII, and prothrombin mutation) interact synergistically to increase the risk of venous thrombosis (Bloemenkamp 2003; Huerta 2007; Naess 2007).

Venous thrombosis in women has an incidence of 1.6 per 1000 person-years. Incidence rates increase with age: women aged 30 to 34 years show an incidence of 0.25 per 1000 person-years and women aged 60 to 64 years, 0.93 per 1000 person-years (Naess 2007). Others have estimated the incidence in women during the reproductive years to be in the range of 0.5 to 1.0 per 1000 person-years (Heinemann 2007). Despite the low incidence of venous thrombosis among women of reproductive age, the impact of oral contraceptives on the risk is large since it is estimated that more than 100 million women worldwide use an oral contraceptive (WHO 1998). Moreover, venous thrombosis is associated with an

increased mortality risk. Overall, the 30-day case fatality rate is higher in patients with pulmonary embolism than in those with DVT (9.7% to 12% versus 4.6% to 6%) (White 2003; Huerta 2007; Naess 2007). In women from 15 to 44 years of age the venous thrombosis-associated mortality rate is lower (0.6% to 1.7%) (Lidegaard 1998b).

DVT may damage deep venous valves with venous reflux and venous hypertension in the lower limbs, resulting in a post-thrombotic syndrome (PTS). PTS is characterized by pain, heaviness, and swelling of the leg aggravated by standing or walking (Kearon 2003). PTS may develop in half of all DVT patients within three months, with no further increase being seen up to two years of follow-up (Tick 2010). Complete resolution of pulmonary embolism occurs in about two-thirds of patients, with partial resolution in the remainder. However, chronic thromboembolic pulmonary hypertension may occur in up to 5% of pulmonary embolism patients (Kearon 2003).

Description of the intervention

The first combined oral contraceptive (COC) was introduced in 1960 (Enovid®). It consisted of 0.15 mg mestranol, an estrogen, and 9.85 mg norethynodrel, a progestogen. Shortly after, the first case of venous thrombosis associated with COC was reported (Jordan 1961). Since then many studies have established the association between COC use and occurrence of venous thrombosis (van Hylckama Vlieg 2011).

Several large studies in the 1990s confirmed a two- to four-fold increase in the risk of venous thrombosis associated with COC use (Thorogood 1992; Vandenbroucke 1994; WHO 1995; Farmer 1997). Since the estrogen compound in COC was thought to cause the increased risk, the dose of estrogen has been gradually lowered from 150 to 100 µg to 20 µg in the 1970s (Stolley 1975; Wharton 1988; Thorogood 1993). The lower dose of ethinylestradiol in contraceptives was indeed associated with a reduction in the venous thrombosis risk (Inman 1970; Meade 1980; Vessey 1986; WHO 1995; Lidegaard 2002). The oral contraceptives currently prescribed which contain 30 µg of ethinylestradiol are associated with a higher risk of venous thrombosis than contraceptives containing 20 µg (Lidegaard 2009; van Hylckama Vlieg 2009).

Besides adjustments in the dose of ethinylestradiol, the progestogen compound was changed to reduce the side effects of the COC. After the first-generation progestogens, new progestogens were developed in the 1970s and 1980s (second and third-generation progestogens, respectively). It was shown that third-generation COC users had a higher risk of venous thrombosis than second-generation users (Kemmeren 2001; Vandenbroucke 2001; Lidegaard 2009; van Hylckama Vlieg 2009). However, these results were disputed: it was reasoned that bias or confounding could explain the difference in venous thrombosis risk between the progestogen generations. These issues were addressed in an opinion article and a meta-analysis in which it was shown that the pres-

ence of bias or confounding could not explain the observed results (Vandenbroucke 1997; Kemmeren 2001).

Other progestogens have been developed since the introduction of the third-generation progestogens, i.e., drospirenone (2001) and dienogest (1995). The use of drospirenone in a COC has been shown to increase the risk of venous thrombosis (Lidegaard 2009; van Hylckama Vlieg 2009), compared with non-use and compared with second-generation contraceptives (Jick 2011; Parkin 2011). However, no information concerning the risk of venous thrombosis is available for the contraceptive containing dienogest, mainly used in Germany (Kuhl 1998).

How the intervention might work

The use of COCs affects hemostasis in many ways. It increases factors involved in coagulation or indicative of increased activity of this system (i.e., factor II, factor VII, and factor VIII, prothrombin fragment 1+2, D-Dimer). Natural anticoagulant factors are also affected, for example, the anticoagulant protein C is increased whereas other anticoagulation factors are decreased (i.e., antithrombin and protein S) in COC users. This trend is more pronounced in third-generation COC users than in second-generation users (Vandenbroucke 2001; Kemmeren 2002a; Kemmeren 2002b; Kemmeren 2004).

Besides these individual coagulation factors, the measurement of activated protein C (APC) resistance provides insight into the overall balance of coagulation (Vandenbroucke 2001). There are two APC resistance assays for probing the plasma response to APC (the endogenous thrombin potential assay and the activated partial thromboplastin time (APTT)-based assay). The two assays rely on different coagulation triggers and endpoints and they probe different coagulation reactions. In summary, APC resistance evaluates the relative inability of protein C to cleave activated factors V and VIII leading to a prothrombotic state (Vandenbroucke 2001; Castoldi 2010). APC resistance predicts venous thrombosis risk in men and in women, as well as in COC users and non-users (Tans 2003). Several studies have confirmed that APC resistance is increased in COC users (Kemmeren 2004; Rad 2006; Kluit 2008) and the effect is more pronounced in users of a third-generation progestogen than with a second-generation progestogen (Kemmeren 2004).

Why it is important to do this review

Since the introduction of the third-generation progestogens, new progestogens have been introduced, such as nestorone, dienogest, norgestrol acetate and spiro lactone derivatives, trimegestone, and drospirenone (Sitruk-Ware 2006). Many studies compare these new COCs to a COC containing levonorgestrel, which is assumed to have the lowest risk of venous thrombosis (Gomes 2004; Jick 2011; Lidegaard 2011). We set out to review the association be-

tween COC and risk of venous thrombosis at the level of different COCs, including the potential risk associated with COCs containing new progestogens. Specifically, we performed a network meta-analysis to compare one COC to another or to non-use. Network meta-analysis allows not only the comparison of two treatments but also a simultaneous comparison of several competing treatments, even where few or no direct comparisons exist. In addition, assessment of effect may be more realistic because it is based on a much larger body of evidence than in conventional meta-analysis (Jansen 2008; Thijs 2008). In this network analysis we took into account not only the progestogen used in the COC but also the estrogen dose. The rationale of the present systematic review is to provide an update on the venous thrombosis risk associated with COC formulations and to perform a network meta-analysis on the estrogen dosage and progestogen component of COCs. The systematic review protocol was established before we developed the review that was published in September 2013 (Stegeman 2013). Reasons for not publishing the protocol before publication of the review were publication rights and unity between the protocol and *The Cochrane Library/BMJ* review. For abbreviations, we refer to Table 1.

OBJECTIVES

The objectives of this review are:

1. to estimate venous thrombosis risk associated with COC use compared with non-use;
2. to perform a network comparison of the risk associated with the three generations of COCs;
3. to compare the effect of estrogen doses and types of progestogen on venous thrombosis risk.

METHODS

Criteria for considering studies for this review

Types of studies

Observational studies on adverse effects may provide valid evidence on unintended effects of treatment as they are often unpredictable and not linked to indications for treatment (Vandenbroucke 2004; Vandenbroucke 2006; Vandenbroucke 2008). Empirical evidence suggests that there may be no difference on average in side effects risk estimates of an intervention derived from meta-analyses of randomized controlled trials (RCT)

and meta-analyses of observational studies. Therefore it seems reasonable not to restrict systematic reviews of adverse effects only to a specific study type (Golder 2011) and also because there is a paucity of experimental data on side effects. Thus, systematic reviews on the harms of interventions often come from observational studies. Observational studies in this review included case-control, cohort, and nested case-control designs. If available, RCTs would also be evaluated and included. Study design criteria are described in Table 2 and Table 3.

Types of participants

Participants were healthy women taking a COC. We excluded studies of women on postmenopausal hormone replacement therapy, studies of women taking non-oral or progestogen-only contraceptives, and studies of women with venous thrombosis recurrence.

Types of interventions

COC use was compared with non-use or with a reference COC (for example, levonorgestrel with 30 µg of ethinylestradiol). We defined a woman as a COC non-user when either she had never been exposed to a COC or she was a former/previous COC user. As there is no generally accepted way to classify COC according to generation of progestogen, we classified as 'first-generation' COCs those including lynestrenol and norethisterone as progestogens. 'Second-generation' COCs included norgestrel and levonorgestrel, while 'third-generation' COCs included desogestrel, gestodene, or norgestimate as progestogens. Therefore, we classified COCs by progestogen generation independently of ethinylestradiol dose. Whenever another COC generation classification was employed by the researchers, we also kept the original generation classification data so we could evaluate the effect of COC generation classification on venous thrombosis risk (Henzl 2000; Sitruk-Ware 2008). We also categorized COCs according to estrogen dose and to progestogen type.

Types of outcome measures

The outcome was fatal or non-fatal first venous thrombosis event (DVT or pulmonary embolism). We classified outcomes according to diagnostic criteria as:

1. strict diagnostic outcome and specified criteria for venous thrombosis;
2. discharge diagnoses from wards, but without a priori specified outcome criteria;
3. ad hoc outcome selection of venous thrombosis patients not specified in advance.

We included these outcome measures in the data abstraction form and we evaluated them in a sensitivity analysis. The outcome classification was assessed independently by two review authors (MdB, BHS) and disagreements were resolved by consensus.

Primary outcomes

The primary outcome was fatal or non-fatal first venous thrombosis event (DVT or pulmonary embolism).

Secondary outcomes

Not applicable.

Search methods for identification of studies

The search was created in association with an expert librarian (JW Schoones, Walaeus Library, LUMC, Leiden, NL). The search strategy is shown in [Appendix 1](#).

Electronic searches

We have searched the following databases: the Cochrane Database of Systematic Reviews (1988 to 22 April 2013), MEDLINE (1966 to 22 April 2013), EMBASE (1980 to 22 April 2013), Web of Science (1900 to 22 April 2013), CINAHL (1982 to 22 April 2013), Academic Search Premier (1997 to 22 April 2013), and ScienceDirect (1995 to 22 April 2013). We have amended the search strategy for each database. We have not set a language restriction on the study search.

Searching other resources

In addition, we checked the references of the selected studies and of any reviews identified.

Data collection and analysis

We analyzed the study results by comparing the venous thrombosis relative risk between COC users and non-users and comparing different types and dosing of COC components based on a network meta-analysis.

We used standard piloted forms for study selection, 'Risk of bias' assessment, and data abstraction. Study selection forms included study identification, inclusion/exclusion criteria, standard study design classification, intervention and outcome evaluation, exposure ascertainment, and completeness of results.

Selection of studies

Two review authors (MdB, BHS) independently evaluated the title and abstract of each study in the study search for study retrieval using standard piloted forms and specific inclusion and exclusion criteria. Disagreements have been resolved by consensus and a third author (OMD) was consulted if disagreement persisted.

Data extraction and management

Two review authors (MdB, BHS) independently performed data extraction using standard, piloted forms. We extracted details of methods (i.e., participants, age), intervention/exposure (i.e., hormone type, dosage, exposure ascertainment), study comparison, outcome criteria assessment (as defined in [Types of outcome measures](#) section), results (i.e., number of participants, sample size, number of events, adjusted and unadjusted measure of effect, absolute risk evaluation), and other variables (i.e., funding source, first time users). Any disagreements were resolved by discussion and a third author (OMD) was consulted if disagreement persisted.

Assessment of risk of bias in included studies

Tools for assessing quality in clinical trials are well-described but much less attention has been given to similar tools for observational studies. Although the Newcastle-Ottawa tool is frequently used to assess observational studies, the reliability or validity is unknown ([Deeks 2003](#); [Sanderson 2007](#)). Since the Newcastle-Ottawa tool is not customized for case-control study designs, and as many case-control studies of COCs are available, we have customized a version of the Newcastle-Ottawa tool for the research question ([Higgins 2011](#)). According to study design (case-control or cohort designs), slightly different 'Risk of bias' assessment questions were customized:

1. For participant selection in case-control study designs and outcome assessment in cohort study designs, we customized the following question: 'Was there a (pre)defined outcome assessment?' Possible options include 'Venous thrombosis objectively confirmed in all included cases'; 'Not all venous thrombosis objectively confirmed'; and 'Unclear'. The criteria for venous thrombosis objectively confirmed include DVT event diagnosed by plethysmography, ultrasound examination, computed tomographic scanning, magnetic resonance imaging (MRI), or venography; or when a pulmonary embolism event was diagnosed by ventilation-perfusion (V/Q) scanning, multidetector helical computed axial tomography (CT), or pulmonary angiography ([Goodacre 2006](#); [Qaseem 2007](#)), or by other strict diagnostic and specified criteria for venous thrombosis. Low risk of bias is defined as venous thrombosis reported as objectively confirmed in all cases.

2. For participant selection in case-control studies we customized the question: 'Was the control sampling adequate?' Possible options include 'Yes, with controls truly representing the source population (community controls)'; 'No, with controls not representing the source population'; 'Unclear'. In cohort studies we customized the question: 'Was the selection of the non-exposed cohort adequately performed?' Possible options include 'Drawn from the same community as the exposed cohort'; 'Drawn from a different source'; 'No description of the derivation of the non-exposed cohort'. This item was assessed when the

control or the non-exposed participants were derived from the same population as the cases or the exposed participants. Low risk of bias is defined as a study with controls or non-exposed participants sampled from the source population or from the same community as exposed participants, respectively.

3. For both study designs, we customized a question evaluating whether or not there were adjustments for confounding performed either in the analysis or by design (matching). Low risk of bias is defined as adjustment for age and calendar time.

4. Regarding exposure evaluation, the customized question for both study designs was: 'Was COC utilization properly assessed?' Possible options for case-control study designs include 'Database record' (i.e., drug deliverance records); 'Interview not blinded to case/control status'; 'Written self report or medical record only'; and 'No description'. For cohort study designs, the options include: 'Database record' (i.e., COC prescription deliverance records); 'Structured interview with interviewer blinded'; 'Written self report'; and 'No description'. Low risk of bias is defined as a database record selection or written self report in cohort design.

5. For cohort study designs, we customized a further question regarding the possibility of loss to follow-up. Possible options include 'complete follow-up' (i.e., all participants accounted for); 'Participants lost to follow-up unlikely to introduce bias' (i.e., less than 10% of the trial population lost to follow-up); 'Follow-up rate potentially leading to bias' (i.e., more than 10% of the trial population lost to follow-up); and 'No statement'. So, for this question, the cut-off point was 10% and low risk of bias is defined as studies with complete or over 90% follow-up (Kristman 2005).

We did not use the 'Risk of bias' assessment to accept or reject studies. However, we produced a table describing 'Risk of bias' assessment for the included studies. Two independent review authors (MdB, BHS) assessed risk of bias using a standard piloted form. Any persistent disagreement was resolved by discussion with a third author (OMD).

Measures of treatment effect

We extracted effect estimates from observational studies or RCTs. Effect estimates can be either odds ratios (RCT, cohort studies, and case-control studies) or risk ratios (RCT and cohort studies). We extracted or recalculated accompanying 95% confidence intervals based on standard errors or P values.

Unit of analysis issues

The unit of analysis was a healthy women using COC specified by ethinylestradiol dose and progestogen type.

Dealing with missing data

The denominator for each outcome in each study was the number of participants minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

For heterogeneity calculation we used the standard deviation/variance of the effect between studies. We explored possible reasons for heterogeneity (i.e., participants and intervention) whenever the number of studies allowed. Study class with 0 (zero) events was inflated to 0.5. Indirect comparisons used a random-effects model. We considered results heterogeneous whenever homogeneity is unlikely, that is a low P value (< 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

We investigated reporting biases (such as publication bias) using a funnel plot. After visual inspection for asymmetry we used the linear regression test for asymmetry proposed by Egger (Egger 1997).

Data synthesis

We calculated the meta-analysis adjusted odds ratios by pooling adjusted odds ratios from individual studies, weighting individual study results by the inverse of their variance. For included studies, we noted levels of attrition.

When we did not find explanations for heterogeneity, we considered using a random-effects model with appropriate cautious interpretation. We used tables for graphical representation of the individual study point estimates and their associated 95% CI.

For the network meta-analysis, we selected study categories for comparisons whenever there was at least one study with a specific comparison between estrogen dose or progestogen type. One can calculate indirect comparisons between two strategies by examining studies that contrast each strategy against a third 'reference' intervention. We first derived pooled estimates from standard direct ('head-to-head') comparisons and then undertook indirect comparisons for estrogen dosing and progestogen type evaluations. We estimated the comparisons in a pair-wise manner combining all direct ('head-to-head') and indirect evidence in a single joint analysis (network meta-analysis), using a log odds model with a random-effects model. Graphic representation of the results was made by a matrix representing each comparison.

The extent of disagreement between direct and indirect evidence was also quantified by the incoherence of the network (Thijs 2008). We also performed a meta-analysis comparing COCs by progestogen generation. We performed the statistical analyses, including the network analysis, with a STATA package (Stata 2011).

Subgroup analysis and investigation of heterogeneity

To explore substantial heterogeneity, we performed subgroup analysis and sensitivity analysis (study design and funding). Funding is defined as any study receiving money from pharmaceutical companies.

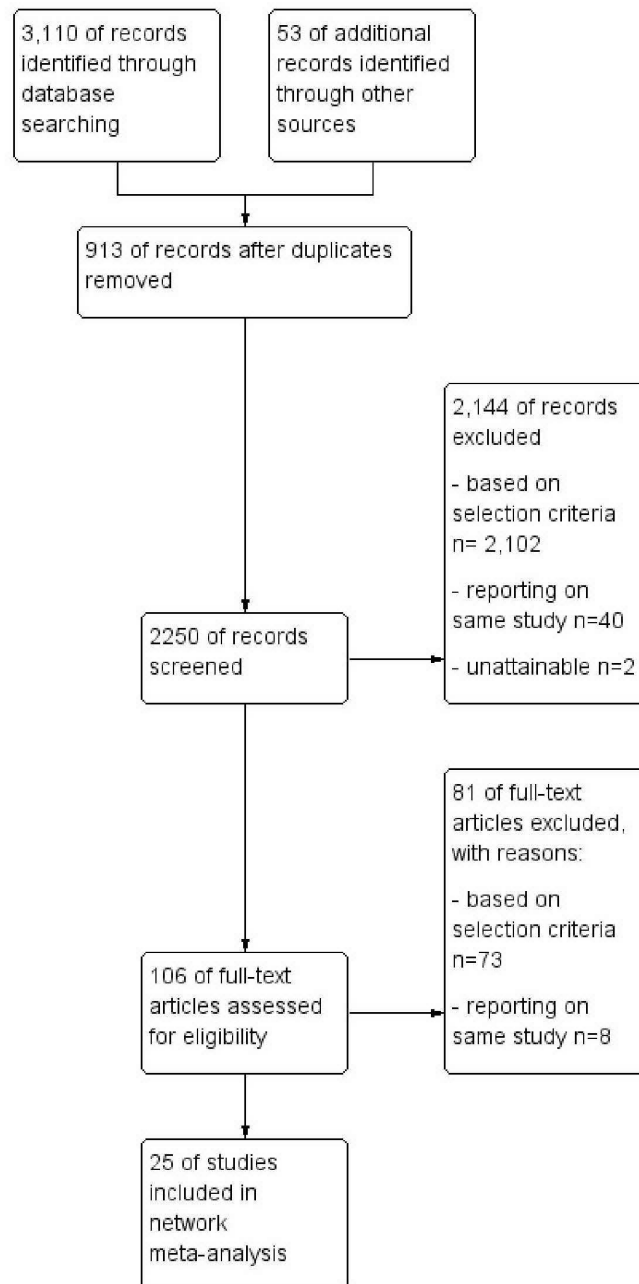
Sensitivity analysis

We carried out sensitivity analyses to explore heterogeneity regarding study design, outcome certainty (venous thrombosis objectively confirmed), and source of funding. To determine the stability of the overall risk estimate, we performed sensitivity analysis in which each design, outcome, and funding source category was individually observed by progestogen generation.

RESULTS**Description of studies**

Of 3163 publications retrieved through electronic and references searches, 2144 were excluded after screening the title and abstract and 81 were excluded after detailed assessment of the full text ([Figure 1](#)). Overall, 26 studies reported in 25 articles were included (one article ([WHO 1995a](#)) presented two studies, see [Characteristics of included studies](#)). Two publications provided important additional information to studies included in the meta-analysis (information on first time use); data from these publications were added to the respective studies already included.

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Figure 1. Study flow diagram.

Nine cohort studies, three nested case-control studies, and 14 case-control studies were included. Studies were published between 1995 and 2013 and including participants from 1965 to 2009. 19 studies were conducted in Europe, three in the United States of America, one in Israel, one in New Zealand, one in developing countries and one study in several countries across the world. Twelve studies used strict and specific diagnosis criteria for VT events and eight studies were industry-funded.

Two studies (Lidegaard 2011, Samuelsson 2004) reported the absolute risk of venous thrombosis in non-users: 0.19 and 0.37 per 1000 woman years. Based on data from 15 studies that included a

non-user group, use of combined oral contraceptives was found to increase the risk of venous thrombosis fourfold (relative risk 3.5, 95% confidence interval 2.9 to 4.3).

Risk of bias in included studies

Eight studies assessed combined oral contraceptive use through an interview or questionnaire (Figure 2). Only five studies objectively confirmed venous thrombosis in all patients, whereas five case-control studies selected controls from a population in hospital care. Of the nine cohort studies, none provided information about loss to follow-up.

Figure 2. Overview of the risk of bias per study

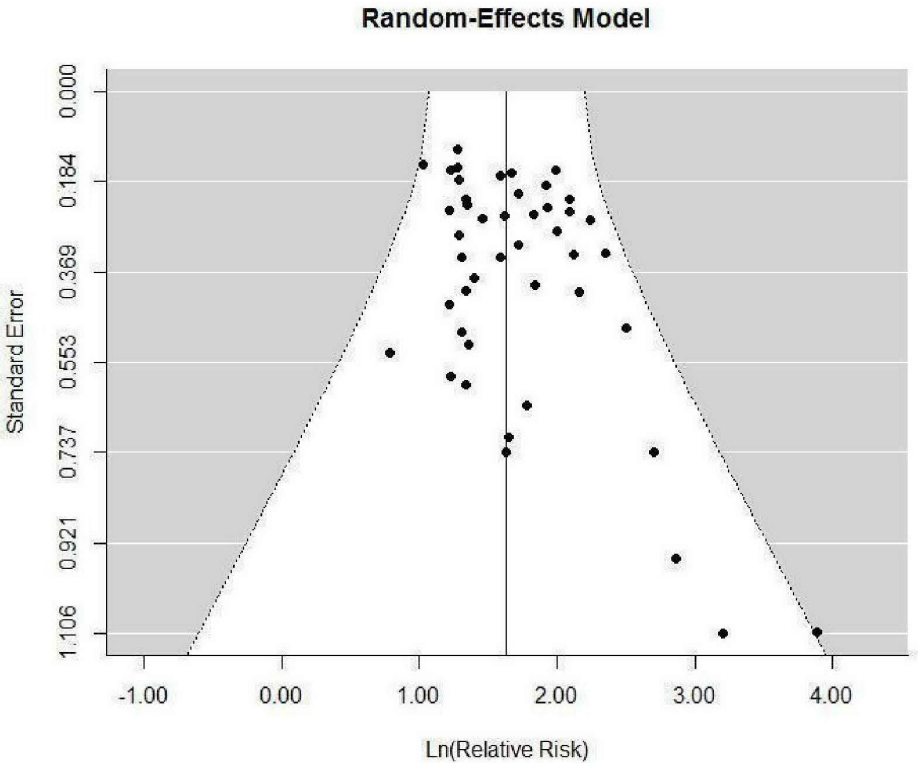
Author	Year	Source population	OC assessment	Outcome assessment	Follow-up
B.S. Andersen	1998	Low	Low	Low	NA
S.T. Bird	2013	NA	Low	High	?
K.W.M. Bloemenkamp	1995	Low	High	Low	NA
K.W.M. Bloemenkamp	1999	Low	High	Low	NA
R. Farmer	1996	NA	Low	?	?
R.D.T. Farmer	1998	Low	Low	?	NA
R.D.T. Farmer	2000	NA	Low	High	?
N. Gronich	2011	NA	Low	?	?
K. Hedenmalm	2004	NA	Low	High	?
L.A.J. Heinemann	2002	High	High	High	NA
L.A.J. Heinemann	2010	Low	High	High	NA
R.M.C. Herings	1999	NA	Low	?	?
A. van Hylckama Vlieg	2009	Low	High	Low	NA
S.S. Jick	2006	Low	Low	?	NA
S.S. Jick	2011	Low	Low	?	NA
M.A. Lewis	1996	High	High	?	NA
Ø. Lidegaard	2002	Low	High	High	NA
Ø. Lidegaard	2011	NA	Low	High	?
I. Martinelli	1999	Low	?	?	NA
L. Parkin	2000	Low	High	High	NA
L. Parkin	2011	Low	Low	High	NA
E. Samuelsson	2004	NA	Low	Low	?
J.C. Todd	1999	NA	Low	High	?
WHO	1995	High	Low	High	NA
WHO1	1995	High	Low	High	NA
WHO2	1995	High	Low	High	NA

High risk	High
Low risk	Low
Unclear	?
NA	NA, not applicable due to cohort design in case of source population or due to case-control design in case of follow-up

Selective reporting

Neither the funnel plot of the comparison arms of studies (Figure 3) nor the linear regression test as proposed by Egger (p-value=0.22) suggested asymmetry.

Figure 3. Funnel plot of studies of combined oral contraceptive use and venous thrombosis risk



Effects of interventions

Network meta-analysis comparing generations of progestogens

A total of 23 studies were included for the analysis stratified per generation of progestogen. Three studies (Bird 2013, Jick 2011, Parkin 2011) reported solely on the risk of venous thrombosis in drospirenone, which is not classified as a generation of progestogen. Table 4 provides details of the number of events and total number of women or total follow-up time per generation, and

Table 5 provides the study specific adjusted risk estimates. Table 6 shows results of the network meta-analysis according to generations of progestogen. Compared with non-users, the risk of venous thrombosis in users of oral contraceptives with a first generation progestogen increased 3.2-fold (95% confidence interval 2.0 to 5.1), 2.8-fold (2.0 to 4.1) for second generation progestogens, and 3.8-fold (2.7 to 5.4) for third generation progestogens. The risk of venous thrombosis in second generation progestogen users was similar to the risk in first generation users (relative risk 0.9, 0.6 to 1.4). Third genera-

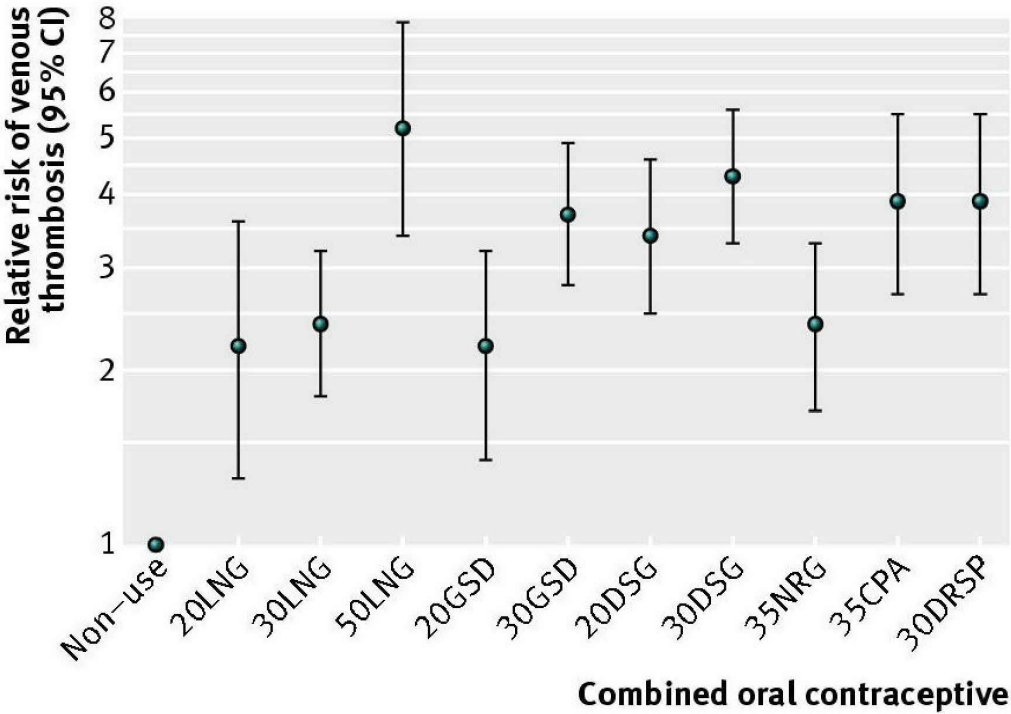
tion users had a slightly higher risk than second generation users (1.3, 1.0 to 1.8). Restricted to studies with an identical classification of generations (see methods section for classification used), the results of each generation compared with non-use remained the same (first generation relative risk 3.2, 95% confidence interval 1.6 to 6.4; second generation 2.6, 1.5 to 4.7; third generation 3.5, 2.0 to 6.1). A formal interaction test did not show inconsistencies in the network ($\chi^2=2.97$, $P=0.71$).

Network meta-analysis comparing different combined oral contraceptives

Of 14 studies providing data per type of oral contraceptive (Table 7, Table 8, Table 9, Table 10), at least one preparation was com-

pared with non-use or two types were compared directly. Table 11 shows results of the analysis. All preparations were associated with a more than twofold increased risk of venous thrombosis compared with non-use (Figure 4). The relative risk estimate was highest in 50LNG users and lowest in 20LNG and 20GSD users. A dose related effect was observed for gestodene, desogestrel, and levonorgestrel, with higher doses being associated with higher thrombosis risk. The risk of venous thrombosis for 35CPA and 30DRSP was similar to the risk for 30DSG (relative risk 0.9, 95% confidence interval 0.6 to 1.3 and 0.9, 0.7 to 1.3, respectively, compared with 30DSG). A formal interaction test could not be performed because only two of 14 studies provided data for exactly the same contraceptives.

Figure 4. Network meta-analysis, per contraceptive plotted on a logarithmic scale. Dots (lines)=overall relative risk (95% confidence interval) of venous thrombosis; non-use=reference group.



Sensitivity analyses

We performed sensitivity analyses according to funding source, study design, and method of diagnosis confirmation (objective vs subjective confirmation of venous thrombosis). Table 12 shows

the results from the sensitivity analysis. Sensitivity analysis stratified by funding source showed that the risk estimate for third generation users (compared with non-users) was lower in industry sponsored studies than in non-industry sponsored studies (relative

risk 1.9 v 5.2). In cohort studies, the risk estimate for third generation users (compared with non-users) was lower than the risk for third generation users in case-control studies (2.0 v 4.2). All risk estimates were higher in studies with objectively confirmed venous thrombosis, of which none were industry sponsored.

DISCUSSION

Summary of main results

We performed a network meta-analysis based on 26 studies. Overall, combined oral contraceptive use increased the risk of venous thrombosis fourfold. The reported incidence of venous thrombosis in non-users was in line with the literature. We observed that all generations of progestogens were associated with an increased risk of venous thrombosis and that third generation users had a slight increased risk compared with second generation users. All individual types of combined oral contraceptives increased thrombosis risk compared with non-use more than two-fold. The highest risk of venous thrombosis was found among 50LNG users, and the risk was similar in 30DRSP, 35CPA, and 30DSG users. Users of 30LNG, 20LNG, and 20GSD had the lowest thrombosis risk.

Quality of the evidence

See under [Potential biases in the review process](#) and [Figure 2](#).

Potential biases in the review process

A network meta-analysis summarises data from direct and indirect comparisons in a weighted average. In the present study, this resulted in a comprehensive overview of the risk of venous thrombosis in frequently prescribed combined oral contraceptives. The internal validity of the network meta-analysis was assessed through interaction analysis modelling potential inconsistencies in the network ([White 2012](#)). Our results of the analysis based on generations of progestogens indicated that potential inconsistencies are likely the result of chance.

A limitation of our network meta-analysis was that publications had to provide the crude number of users and number of events per type of combined oral contraceptive. A total of 15 studies provided information on combined oral contraceptive use and thrombosis risk without specification of which contraceptive preparations were used. These studies could therefore not be included. Because of the need for crude numbers in the network meta-analysis, adjusted risk estimates were not used for pooling the data. Confounding could have influenced our results. Age is a potential confounder for the association between contraceptive use and venous thrombosis. Women using second generation contraceptives are generally older than users of third generation contraceptives. If an analysis is not adjusted for age, the relative risk will then

underestimate the risk of venous thrombosis in users of third generation contraceptives compared with users of second generation contraceptives. This implies that the risk of third generation users may be higher than reported here. However, age was often dealt with in the design of the studies. Body mass index is only weakly associated with combined oral contraceptive use, and analyses unadjusted for body mass index are probably not confounded.

There is no generally accepted way to classify oral contraceptives according to generations of progestogens. For instance, norgestimate can be categorised as a second or a third generation progestogen. As a consequence, the classification of these generations was not the same in every publication. However, the results did not materially change when restricted to studies with an identical classification of generations as described in the methods nor when contraceptives with

desogestrel or gestodene were compared with levonorgestrel (that is, norgestimate was not taken into account when classifying contraceptives into generations) (data not shown).

In the classification of progestogen generations used in this meta-analysis, the dose of ethinylestradiol was not taken into account. The observed increased risk in third generation contraceptives, compared with second generation contraceptives, cannot be explained by a difference in ethinylestradiol dose because a higher dose of ethinylestradiol (50 µg) can be present in a second generation contraceptive but not in a third generation contraceptive.

In only a few included studies, venous thrombosis was objectively confirmed in all patients. Only about 30% of patients with clinical symptoms of thrombosis are diagnosed with venous thrombosis ([Wells 1995](#)). Including patients without objectively confirmed venous thrombosis would lead to overestimating the association when oral contraceptives users were more likely to be diagnosed than non-users (diagnostic suspicion bias). However, two studies showed that this bias was independent of type of oral contraceptive ([Kemmeren 2001](#), [Vandenbroucke 1997](#)). In studies without objective confirmation, women were misclassified irrespective of their contraceptive use, leading to non-differential misclassification. Therefore, results of such studies may underestimate the true association, which was confirmed by our sensitivity analysis where the risk estimates were higher in studies with objectively confirmed venous thrombosis than in those without an objective confirmation.

Agreements and disagreements with other studies or reviews

Two other meta-analyses ([Kemmeren 2001](#), [Manzoli 2012](#)) have evaluated the risk of venous thrombosis comparing third generation contraceptive users with second generation users. Both studies found an increased risk in third generation users (relative risk 1.5, 95% confidence interval 1.2 to 1.8 and 1.57, 1.24 to 1.98 53, respectively), which are in line with our results. The majority of included studies from both meta-analyses were included in our

analysis.

AUTHORS' CONCLUSIONS

Implications for practice

All individual types of combined oral contraceptives increased thrombosis risk compared with non-use more than two-fold. The highest risk of venous thrombosis was found among 50LNG users, and the risk was similar in 30DRSP, 35CPA, and 30DSG users. Users of 30LNG, 20LNG, and 20GSD had the lowest thrombosis risk.

It should be kept in mind that all combined oral contraceptives increase the risk of venous thrombosis, which is not the case for the levonorgestrel intrauterine device (van Hylckama Vlieg 2010). However, if a woman prefers using combined oral contraceptives, only contraceptives with the lowest risk of venous thrombosis and good compliance (Gallo 2013) should be prescribed, such as levonorgestrel with 30µg ethinylestradiol. Current practice is to increase the dose of ethinylestradiol in case of disruptions in bleeding patterns (Gallo 2013). Our results indicate that prescribing 50LNG in case of spotting during the use of 30LNG might carry a serious risk for venous thrombosis.

Combining different preparations of oral contraceptive into generations of progestogens may not be an appropriate way to present the risk of thrombosis, because the risk depends on the dose of

ethinylestradiol as well as on the progestogen provided. We suggest abstaining from any classification of contraceptives, but to compare the risk of venous thrombosis per oral contraceptive preparation.

Implications for research

Although we observed that the risk of venous thrombosis increased with the dose of ethinylestradiol, this seemed to depend on the progestogen provided. There was no difference in the venous thrombosis risk between 20LNG and 30LNG, whereas a difference in the risk was observed between 20DSG and 30DSG, for example. It is unclear why the dose effect of ethinylestradiol might depend on the progestogen. A possibility is that there is a difference in inhibitory effects of the progestogen on the procoagulant effect of ethinylestradiol. Oral contraceptive use increases the levels of factors II, VII, VIII, protein C, and decreases the levels of antithrombin, tissue factor pathway inhibitor, and protein S. Clinical studies have showed that this effect on coagulation factors was more pronounced in desogestrel users than in levonorgestrel users, and limited to combined oral contraceptives (Kemmeren 2002b, Kemmeren 2004).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES**Characteristics of included studies** *[ordered by study ID]***Andersen 1998**

Methods	Case control study
Participants	67 cases / 134 controls (hospital discharge) diagnosis: anticoagulation
Interventions	3rd generation
Outcomes	Events during 3rd generation: 16 / 23. Non-use: 27 / 133. Adjustment for confounding: yes (matched)
Notes	Denmark

Bird 2013

Methods	cohort study
Participants	2001-2009 432,178 women / 263,902 women years (healthcare plan) age: 18-46 y diagnosis: anticoagulation
Interventions	2nd generation and Drospirenone
Outcomes	Events during 2nd generation: 118 / 132,681. Drospirenone: 236 / 131,221 Adjustment for confounding: yes
Notes	USA

Bloemenkamp 1995

Methods	case control study
Participants	1988-1995 126 cases / 159 controls (community based) age: 15-49 y diagnosis: anticoagulation
Interventions	1st, 2nd and 3rd generation
Outcomes	Events during 1st generation: 8 / 13; 2nd generation 20 / 38; 3rd generation 37 / 52. Non-use: 46 / 150 Adjustment for confounding: yes

Bloemenkamp 1995 (Continued)

Notes	The Netherlands
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Bloemenkamp 1999	
Methods	case control study
Participants	1982-1995 185 cases / 591 controls (community based) age: 15-49 y diagnosis: anticoagulation
Interventions	1st, 2nd and 3rd generation
Outcomes	Events during 1st generation: 18 / 46; 2nd generation 8 / 22; 3rd generation 33 / 67. Non-use: 83 / 511 Adjustment for confounding: yes
Notes	The Netherlands

Farmer 1996

Methods	cohort study
Participants	30 cases / 697,000 women (general practioners database) age 14-45 y diagnosis: anticoagulation
Interventions	2nd and 3rd generation
Outcomes	Events using during 2nd generation 14 / 76,600; 3rd generation 15 / 65,100 Adjustment for confounding: yes
Notes	United Kingdom

Farmer 1998

Methods	case control study
Participants	1992-1995 42 cases / 168 controls (healthcare plan) age: 18-49 y diagnosis: anticoagulation
Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 27 / 116; 3rd generation 15 / 79 Adjustment for confounding: yes (matched)

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Farmer 1998 *(Continued)*

Notes	Germany
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Farmer 2000

Methods	cohort study
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Participants	1992-1997 287 cases / 783,876 women years (prescription database) age: 15-49 y diagnosis: ad hoc
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Interventions	1st, 2nd and 3rd generation
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Outcomes	Events during 1st generation: 12 / 39,421; 2nd generation 98 / 307,070; 3rd generation 161 / 374,129 Adjustment for confounding: no
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Notes	United Kingdom ('General Practice Research Database', GRPD)
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Gronich 2011

Methods	cohort study
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Participants	2002-2008 329,995 women / 819,749 women years (healthcare plan) age: 12-50 y diagnosis: ad hoc
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Interventions	2nd and 3rd generation
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Outcomes	Events during 2nd generation 23 / 33,187; 3rd generation 384 / 651,455 Adjustment for confounding: yes
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Notes	Israel
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Hedenmalm 2004

Methods	cohort study
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Participants	1965-2001 172 cases / 10,016,194 treatment years (community based) diagnosis: medical records
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Interventions	1st, 2nd and 3rd generation
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Outcomes	Events during 1st generation 36 / 1,898,899; 2nd generation 74 / 6,343,562; 3rd generation 83 / 1,739,393 Adjustment for confounding: no
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Hedenmalm 2004 (Continued)

Notes	Sweden
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Heinemann 2002

Methods	case control study
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Participants	1994-1999 606 cases / 2,942 controls (community based) age: 15-49 y diagnosis: clinical criteria
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Interventions	1st, 2nd and 3rd generation
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Outcomes	Events during 1st generation 45 / 190; 2nd generation 131 / 865; 3rd generation 28 / 195. Non-use 246 / 2,115 Adjustment for confounding: yes
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Notes	Germany
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Heinemann 2010

Methods	case control study
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Participants	2002-2006 451 cases / 1,920 controls (community based) age: 15-49 y diagnosis: clinical criteria
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Interventions	2nd and 3rd generation
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Outcomes	Events during 2nd generation 61 / 245; 3rd generation 62 / 238; Non-use 70 / 1,215 Adjustment for confounding: yes
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Notes	Austria
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Herings 1999

Methods	cohort study
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Participants	1986-1995 33 cases / 450,000 women (prescription database) age: 15-49 y diagnosis: ad hoc
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Interventions	2nd and 3rd generation
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Herings 1999 *(Continued)*

Outcomes	Events during 2nd generation 29 / 121,411; 3rd generation 49 / 88,295 Adjustment for confounding: yes
Notes	The Netherlands

Jick 2006

Methods	nested case control study
Participants	2000-2005 281 cases / 1,055 controls (claims database) age: 15-39 y diagnosis: anticoagulation
Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 70 / 386; 3rd generation 211 / 950 Adjustment for confounding: yes (matched)
Notes	USA

Jick 2011

Methods	nested case control study
Participants	2002-2008 186 cases / 681 controls (claims database) age: 15-44 y diagnosis: anticoagulation
Interventions	2nd generation and Drospirenone
Outcomes	Events during 2nd generation: 65 / 433. Drospirenone: 121 / 434 Adjustment for confounding: yes (matched)
Notes	USA

Lewis 1996

Methods	case control study
Participants	1991-1995 505 cases / 1,877 controls (community based) age: 16-45 y diagnosis: clinical symptoms

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Lewis 1996 (Continued)

Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 96 / 419; 3rd generation 156 / 451 Adjustment for confounding: yes (matched)
Notes	UK and Germany ('Transnational study')

Lidegaard 2002

Methods	case control study
Participants	1994-1998 987 cases / 4,054 controls (community based) age: 15-44 y diagnosis: discharges
Interventions	1st, 2nd and 3rd generation
Outcomes	Events during 1st generation 36 / 143; 2nd generation 98 / 296; 3rd generation 351 / 1,204. Non-use 458 / 3,196 Adjustment for confounding: yes (matched)
Notes	Denmark

Lidegaard 2011

Methods	Cohort study
Participants	2001-2009 1,436,310 women / 9,954,925 women years (community based) age: 15-49 y diagnosis: anticoagulation
Interventions	1st, 2nd and 3rd generation, Cyproterone and Drospirenone
Outcomes	Events during 1st generation 21 / 34,203; 2nd generation 198 / 233,912; 3rd generation 1,747 / 2,049,368; Cypro- terone 109 / 120,934; Drospirenone 289 / 309,914. Non-use 1,812 / 4,960,730 Adjustment for confounding: yes
Notes	Denmark

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Martinelli 1999

Methods	case control study
Participants	1995-1998 total number of women was unclear; however, numbers were available for contraceptive of interest (community based) diagnosis: ad hoc
Interventions	3rd generation
Outcomes	Events during 3rd generation 43 / 79. Non-use 41 / 179. Adjustment for confounding: no
Notes	Italy

Parkin 2000

Methods	case control study
Participants	1990-1998 26 cases / 111 controls (general practitioner database) age: not postmenopausal diagnosis: death certificate
Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 3 / 11; 3rd generation 12 / 27. Non-use 9 / 95 Adjustment for confounding: yes
Notes	New Zealand

Parkin 2011

Methods	nested case control study
Participants	2002-2009 61 cases / 215 controls (general practitioners database) age: 15-44 y diagnosis: anticoagulation
Interventions	2nd generation and Drospirenone
Outcomes	Events during 2nd generation 44 / 233; Drospirenone 17 / 43. Adjustment for confounding: yes (matched)
Notes	UK

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Samuelsson 2004

Methods	cohort study
Participants	1991-2000 88 cases / 243,723 women years (adverse events database) age: 15-44 y diagnosis: anticoagulation
Interventions	3rd generation
Outcomes	Events during 3rd generation 17 / 14,819. Non-use 32 / 171,206 Adjustment for confounding: no
Notes	Sweden

Todd 1999

Methods	cohort study
Participants	1992-1997 99 cases / 216,356 women years (healthcare plan) age: 15-49 y diagnosis: anticoagulation
Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 32 / 76,993; 3rd generation 53 / 92,052 Adjustment for confounding: no
Notes	UK

van Hylckama Vlieg 2009

Methods	case control study
Participants	1999-2004 1,525 cases / 1,760 controls (community based) age: <50 y diagnosis: anticoagulation
Interventions	1st, 2nd and 3rd generation
Outcomes	Events during 1st generation 55 / 81; 2nd generation 382 / 672; 3rd generation 412 / 582. Non-use 421 / 1,523 Adjustment for confounding: yes
Notes	The Netherlands

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WHO 1995a

Methods	case control study
Participants	1989-1993 WHO 1 in Europe: 433 cases / 1,044 controls WHO 2 in developing countries: 710 cases / 1,954 controls WHO 1 and 2: community based age: 20-44 y diagnosis: clinical criteria
Interventions	1st, 2nd and 3rd generation
Outcomes	WHO 1: Events during 1st generation 29 / 74; 2nd generation 156 / 392; 3rd generation 53 / 104. Non-use 168 / 855 WHO 2: Events during 1st generation 26 / 65; 2nd generation 153 / 337; 3rd generation 18 / 25. Non-use 505 / 2,220 WHO 1 and 2: adjustment for confounding: yes
Notes	WHO 1: Europe WHO 2: developing countries

WHO 1995b

Methods	case control study
Participants	1989-1993 829 cases / 1,979 controls (community based) diagnosis: clinical criteria
Interventions	2nd and 3rd generation
Outcomes	Events during 2nd generation 137 / 340; 3rd generation 71 / 127. Non-use 397 / 1,916 Adjustment for confounding: yes (matched)
Notes	Brazil, Chile, Colombia, Germany, Hong Kong, Hungary, Jamaica, Thailand, UK

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amundsen 2000	No data on progestagen type or ethinylestradiol dose
Austin 2009	Other hormonal contraceptives, such as transdermal patch, vaginal ring, were included
Barsoum 2010	No data on progestagen type or ethinylestradiol dose

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(Continued)

BCDSP 1973	No data on progestagen type or ethinylestradiol dose
Bergendal 2012	No data on progestagen type or ethinylestradiol dose
Bernstein 1986	No data on progestagen type or ethinylestradiol dose
Bonifacj 1997	Included recurrent venous thrombosis
Bottiger 1980	No data on ethinylestradiol dose
Burnhill 1999	Included progestagen-only contraceptives and retinal vein thrombosis
Diddle 1978	Less than 10 venous thrombosis cases
Dinger 2007	Included recurrent venous thrombosis
Dinger 2010	Included recurrent venous thrombosis
Eng 2008	Compared drospirenone versus other oral contraceptive users
Farmer 1997	Ecologic study
Fuertes 1971	Unclear reference group
Gerstman 1991	Incomplete data on contraceptive use
Girolami 2004	Included not only venous thrombosis
Grodstein 1996	No data on progestagen type or ethinylestradiol dose
Grounds 1974	Included not only venous thrombosis
Hall 2012	No data on venous thrombosis
Hedenmalm 2005	Included recurrent venous thrombosis and cerebral vein thrombosis
Heinemann 2000	Report on Transnational study, already included (Lewis 1996 , Lewis 1999)
Helmrich 1987	Incomplete data on contraceptive use
Herings 1999a	Data already included: Herings 1999
Heuser 2004	No extractable number of exposed and non-exposed women
Hirvonen 1990	No data on progestagen type or ethinylestradiol dose
Huerta 2007	No data on progestagen type or ethinylestradiol dose

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(Continued)

Inman 1968	No data on progestagen type or ethinylestradiol dose
Inman 1970	No data on progestagen type or ethinylestradiol dose
IPPF 1976	Communication to the editor
Kieler 2003	Included recurrent venous thrombosis
Lambrekht 1986	No data on venous thrombosis
Lawrenson 2000	Review
Legnani 2002	Included recurrent venous thrombosis
Lewis 1997	Report on Transnational study, already included (Lewis 1996)
Lewis 1999b	Report on Transnational study, already included: Lewis 1996 , Lewis 1999)
Lewis 1999c	Commentary
Lidegaard 1998a	Updated study see Lidegaard 2002
Lidegaard 1998b	Review
Lidegaard 2001	Review
Lidegaard 2009	Updated study of this 2009 study (Lidegaard 2011) is included
Lindqvist 2009	No data on progestagen type or ethinylestradiol dose
Lis 1993	Publication of study protocol
Ludwig 1970	Unclear what is defined as high progestagen
Martinelli 2003	No data on progestagen type or ethinylestradiol dose
Meade 1980	Included not only venous thrombosis
Meinel 1988	Included not only venous thrombosis and no data on progestagen type or ethinylestradiol dose
Meurer 2001	Review
Nightingale 2000	2000 443 Duplicate report on GPRD (Farmer 2000) and Mediplus Databases (Todd 1999)
Overgaard 1986	No data on progestagen type or ethinylestradiol dose

(Continued)

Pearce 2005	No comparison was included
Petriti 1979	No data on progestagen type or ethinylestradiol dose
Pini 1996	Included not only venous thrombosis and included recurrent venous thrombosis
Porter 1982	Less than 10 venous thrombosis events
Porter 1985	Less than 10 venous thrombosis events
Poulter 1996	Data already included (WHO 1995)
Primignani 2005	Included not only venous thrombosis
Quinn 1992	No data on progestagen type or ethinylestradiol dose
RCPG 1978	Included not only venous thrombosis
Realini 1997	Less than 10 venous thrombosis events
Reed 2012	Compared with other contraceptives
Roach 2013	No data on progestagen type or ethinylestradiol dose
Seaman 2004	Included recurrent venous thrombosis
Seeger 2007	Included recurrent venous thrombosis
Seigel 1969	No data on progestagen type or ethinylestradiol dose
Sidney 2004	Incomplete data on contraceptive use
Spitzer 1993	Publication of study protocol
Stolley 1975	Included not only venous thrombosis
Suissa 1997	Duration of contraceptive use on Transnational study, already included (Lewis 1996 , Lewis 1999)
Thorogood 1992	Included recurrent venous thrombosis and no data on progestagen type or ethinylestradiol dose
Tosetto 2003	No data on progestagen type or ethinylestradiol dose
Tsankova 2010a	Compared ever users versus never users
Tsankova 2010b	No data on progestagen type or ethinylestradiol dose
Ulmer 1997	No data on progestagen type or ethinylestradiol dose

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(Continued)

Vallee 2001	Review
Van der Meer 1997	Review
Vessey 1969	Included recurrent venous thrombosis
Vessey 1986	Incomplete data on contraceptive use
WHO 1989	No data on progestagen type or ethinylestradiol dose
Worralurt 2005	Included recurrent venous thrombosis and no data on progestagen type or ethinylestradiol dose
Yang 2007	Exposed consisted of hormone replacement therapy users and oral contraceptive users

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DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Abbreviations

Specific abbreviations	Explanation
APC	Activated protein C
APTT	Activated partial thromboplastin time
C	Cohort study
CC	Case-control study
COC	Combined oral contraceptive
CT	Computed axial tomography
DVT	Deep-vein thrombosis
MRI	Magnetic resonance imaging
NA	Not applicable
NCC	Nested case-control study
PCS	Prospective cohort study
PTS	Post-thrombotic syndrome
RCT	Randomized controlled trial
V/Q	Ventilation-perfusion
20LNG	20 µg ethinylestradiol with levonorgestrel
30LNG	30 µg ethinylestradiol with levonorgestrel
50LNG	50 µg ethinylestradiol with levonorgestrel
20GSD	20 µg ethinylestradiol with gestodene
30GSD	30 µg ethinylestradiol with gestodene
20DSG	20 µg ethinylestradiol with desogestrel

Table 1. Abbreviations (Continued)

30DSG	30 µg ethinylestradiol with desogestrel
35NRG	35 µg ethinylestradiol with norgestimate
35CPA	35 µg ethinylestradiol with cyproterone acetate
30DRSP	30 µg ethinylestradiol with drospirenone

Table 2. List of study design features

Question and checklist	RCT	PCS	RCS	NCC	CC
<i>Was there a comparison:</i>					
Between two or more groups of participants receiving different interventions?	Y	Y	Y	Y	Y
Within the same group of participants over time?	P	N	N	N	N
<i>Were participants allocated to groups by:</i>					
Concealed randomization?	Y	N	N	N	N
Quasi-randomization?	N	N	N	N	N
Other action of researchers?	N	N	N	N	N
Time differences?	N	N	N	N	N
Location differences?	N	P	P	NA	NA
Treatment decisions?	N	P	P	N	N

Table 2. List of study design features (Continued)

Participants' preferences?	N	P	P	N	N
On the basis of outcome?	N	N	N	Y	Y
Some other process? (specify)					
<i>Which parts of the study were prospective:</i>					
Identification of participants?	Y	Y	N	Y	N
Assessment of baseline and allocation to intervention?	Y	Y	N	Y	N
Assessment of outcomes?	Y	Y	P	Y	N
Generation of hypotheses?	Y	Y	Y	Y	P
<i>On what variables was comparability between groups assessed:</i>					
Potential confounders?	P	P	P	P	P
Baseline assessment of outcome variables?	P	P	P	N	N

RCT = randomized clinical trial
 PCS = prospective cohort study
 RCS = retrospective cohort study
 NCC = nested case-control study
 CC = case-control study
 Y = yes
 N = no
 P = possibly
 NA = not applicable

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Table 3. Checklist for data collection/study assessment

Note: Users need to be very clear about the way in which the terms 'group' and 'cluster' are used in these tables. The above table only refers to groups, which is used in its conventional sense to mean a number of individual participants. With the exception of allocation on the basis of outcome, 'group' can be interpreted synonymously with 'intervention group'. Although individuals are nested in clusters, a cluster does not necessarily represent a fixed collection of individuals. For instance, in cluster-allocated studies, clusters are often studied at two or more time points (periods) with different collections of individuals contributing to the data collected at each time point

Was there a comparison?

Typically, researchers compare two or more groups that receive different interventions; the groups may be studied over the same time period, or over different time periods (see below). Sometimes researchers compare outcomes in just one group but at two time points. It is also possible that researchers may have done both, i.e., studying two or more groups and measuring outcomes at more than one time point

How were participants/clusters allocated to groups?

These items aim to describe how groups were formed. None will apply if the study does not compare two or more groups of participants. The information is often not reported or is difficult to find in a paper. The items provided cover the main ways in which groups may be formed. More than one option may apply to a single study, although some options are mutually exclusive (i.e., a study is either randomized or not)

- Randomization: Allocation was carried out on the basis of truly random sequence. Check carefully whether allocation was adequately concealed until participants were definitively recruited
- Quasi-randomization: Allocation was done on the basis of a pseudo-random sequence, e.g., odd/even hospital number or date of birth, alternation. Note: when such methods are used, the problem is that allocation is rarely concealed
- By other action of researchers: this is a catch-all category and further details should be noted if the researchers report them. Allocation happened as the result of some decision or system applied by the researchers. For example, participants managed in particular 'units' of provision (e.g. wards, general practices) were 'chosen' to receive the intervention and participants managed in other units to receive the control intervention
- Time differences: Recruitment to groups did not occur contemporaneously. For example, in a historically controlled study participants in the control group are typically recruited earlier in time than participants in the intervention group; the intervention is then introduced and participants receiving the intervention are recruited. Both groups are usually recruited in the same setting. If the design was under the control of the researchers, both this option and 'other action of researchers' must be ticked for a single study. If the design 'came about' by the introduction of a new intervention, both this option and 'treatment decisions' must be ticked for a single study
- Location differences: Two or more groups in different geographic areas were compared, and the choice of which area(s) received the intervention and control interventions was not made randomly. So, both this option and 'other action of researchers' could be ticked for a single study
- Treatment decisions: Intervention and control groups were formed by naturally occurring variation in treatment decisions. This option is intended to reflect treatment decisions taken mainly by the clinicians responsible; the following option is intended to reflect treatment decisions made mainly on the basis of participants' preferences. If treatment preferences are uniform for particular provider 'units', or switch over time, both this option and 'location' or 'time' differences should be ticked
- Patient preferences: Intervention and control groups were formed by naturally occurring variation in patients' preferences. This option is intended to reflect treatment decisions made mainly on the basis of patients' preferences; the previous option is intended to reflect treatment decisions taken mainly by the clinicians responsible
- On the basis of outcome: A group of people who experienced a particular outcome of interest were compared with a group of people who did not, i.e., a case-control study. Note: this option should be ticked for papers that report analyses of multiple risk factors for a particular outcome in a large series of participants, i.e. in which the total study population is divided into those who experienced the outcome and those who did not. These studies are much closer to nested case-control studies than cohort studies, even when longitudinal data are collected prospectively for consecutive patients

Which parts of the study were prospective?

These items aim to describe which parts of the study were conducted prospectively. In a randomized controlled trial, all four of these items would be prospective. For non-randomized trials (NRS) it is also possible that all four are prospective, although inadequate detail may be presented to discern this, particularly for generation of hypotheses. In some cohort studies, participants may be identified,

Table 3. Checklist for data collection/study assessment

and have been allocated to treatment retrospectively, but outcomes are ascertained prospectively

On what variables was comparability of groups assessed?

These questions should identify 'before-and-after' studies. Baseline assessment of outcome variables is particularly useful when outcomes are measured on continuous scales, e.g., health status or quality of life

Response options

Try to use only 'Yes', 'No', and 'Can't tell' response options. 'NA' should be used if a study does not report a comparison between groups

Table 4. Included publications with data on generation of progestogens and reference group non-use

Design	Study	Study design	Non-use	1st	2nd	3rd
			n event / n total	n event / n total	n event / n total	n event / n total
1	Bloemenkamp 1995	case control	46 / 150	8 / 13	20 / 38	37 / 52
	Bloemenkamp 1999	case control	83 / 511	18 / 46	8 / 22	33 / 67
	Heinemann 2002	case control	246 / 2,115	45 / 190	131 / 865	28 / 195
	Lidegaard 2011	cohort	1,812 / 4,960,730	21 / 34,203	198 / 233,912	1,747 / 2,049,368
	van Hylckama Vlieg 2009	case control	421 / 1,523	55 / 81	382 / 672	412 / 582
	WHO 1995a WHO 1	case control	168 / 855	29 / 74	156 / 392	53 / 104
	WHO 1995a WHO 2	case control	505 / 2,220	26 / 65	153 / 337	18 / 25
2	Heinemann 2010	case control	70 / 1,215	-	61 / 245	62 / 238
	Lidegaard 2002	case control	458 / 3,196	-	98 / 296	351 / 1,204
	Parkin 2000	case control	9 / 95	-	3 / 11	12 / 27
	WHO 1995b	case control	397 / 1,916	-	137 / 340	71 / 127
3	Andersen 1998	case control	27 / 133	-	-	16 / 23
	Martinelli 1999	case control	41 / 179	-	-	43 / 79
	Samuelsson 2004	cohort	32 / 171,206	-	-	17 / 14,819
4	Farmer 2000	cohort	-	12 / 39,421	98 / 307,070	161 / 374,129

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Table 4. Included publications with data on generation of progestogens and reference group non-use (Continued)

	Hedenmalm 2004	cohort	-	36 / 1,898,899	74 / 6,343,562	83 / 1,739,393
5	Farmer 1996	cohort	-	-	14 / 76,600	15 / 65,100
	Farmer 1998	case control	-	-	27 / 116	15 / 79
	Gronich 2011	cohort	-	-	23 / 33,187	384 / 651,455
	Herings 1999	cohort	-	-	29 / 121,411	49 / 88,295
	Jick 2006	nested case control	-	-	70 / 386	211 / 950
	Lewis 1996	case control	-	-	96 / 419	156 / 451
	Todd 1999	cohort	-	-	32 / 76,993	53 / 92,052

Total can be total number of women in the group, or the total follow-up time

Design refers to the type and number of direct comparisons provided in a single study

Studies with the same design provide direct comparisons of exactly the same generations or same individual oral contraceptives

Total can be total number of women in the group, or the total follow-up time

Design refers to the type and number of direct comparisons provided in a single study

Studies with the same design provide direct comparisons of exactly the same generations or same individual oral contraceptives

Table 5. Study specific adjusted risk estimates: generations of contraceptives

Study	Comparison in RR (95% CI)					
	1st vs non-use	2nd vs non-use	3rd vs non-use	1st vs 2nd	3rd vs 2nd	1st vs 3rd
Andersen 1998	-	-	48.6 (5.6-423)	-	-	-
Bloemenkamp 1995	-	-	-	-	-	-
Bloemenkamp 1999	-	-	-	-	-	-
Farmer 1996	-	-	-	-	-	-
Farmer 1998	-	-	-	-	-	-
Farmer 2000	-	-	-	-	-	-

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Table 5. Study specific adjusted risk estimates: generations of contraceptives *(Continued)*

Gronich 2011	-	-	-	-	-	-
Hedenmalm 2004	-	-	-	-	-	-
Heinemann 2002	8.1 (5.3-12.5)	4.9 (3.5-6.9)	4.3 (2.6-7.2)	-	0.9 (0.6-1.4)	-
Heinemann 2010	-	6.9 (4.3-10.9)	8.1 (5.0-13.1)	-	-	-
Herings 1999	-	-	-	-	3.5 (1.4-8.8)	-
Jick 2006	-	-	-	-	-	-
Lewis 1996	6.2 (3.8-10.2)	3.4 (2.4-4.6)	5.4 (3.9-7.3)	-	1.6 (1.2-2.2)	-
Lidegaard 2002	4.1 (2.4-7.1)	2.9 (2.2-3.8)	4.0 (3.2-4.9)	1.5 (0.9-2.7)	1.3 (1.0-1.8)	-
Lidegaard 2011	-	-	-	-	-	-
Martinelli 1999	-	-	-	-	-	-
Parkin 2000	-	-	-	-	-	-
Samuelsson 2004	-	-	-	-	-	-
Todd 1999	-	-	-	-	-	-
van Hylckama Vlieg 2009	-	-	-	-	-	-
WHO 1995a WHO 1	-	-	-	-	-	-
WHO 1995a WHO 2	-	-	-	-	-	-
WHO 1995b	-	-	-	-	-	-

Table 6. Network meta-analysis, by generation of progestogen used in combined oral contraceptives

	Reference group			
	Non-use	1st	2nd	3rd
Non-use	1	-	-	-
1st	3.2 (2.0-5.1)	1	-	-
2nd	2.8 (2.0-4.1)	0.9 (0.6-1.4)	1	-
3rd	3.8 (2.7-5.4)	1.2 (0.8-1.9)	1.3 (1.0-1.8)	1

Data are in relative risk (95% CI) of venous thrombosis

Data are in relative risk (95% CI) of venous thrombosis

Table 7. Included publications with data on the 3 / 10 selected contraceptives and reference group non-use (see also Table 8)

Design	Study	Study design	Non-use	20 LNG	30 LNG	50 LNG
		n event / n total				
1	van Hylckama Vlieg 2009	Case-control	421 / 1,523	8 / 14	485 / 858	60 / 80
2	Lidegaard 2011	Cohort	1,812 / 4,960,730	-	78 / 104,251	31 / 23,691
3	Parkin 2000	Case-control	9 / 95	-	2 / 6	0 / 2
4	Lidegaard 2002	Case-control	458 / 2,738	-	-	12 / 28
5	Bloemenkamp 1999	Case-control	83 / 511	-	18 / 46	-
6	Bloemenkamp 1995	Case-control	46 / 150	-	20 / 38	-
7	Farmer 2000	Cohort	-	-	64 / 190,191	-
8	Todd 1999	Cohort	-	-	22 / 49,484	-
9	Farmer 1996	Cohort	-	-	5 / 35,800	-
10	Jick 2006	Nested case-control	-	-	70 / 386	-
11	Bird 2013	Cohort	-	30 / 28,782	56 / 58,356	-

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Table 7. Included publications with data on the 3 / 10 selected contraceptives and reference group non-use (see also Table 8)
(Continued)

	Jick 2011	Nested case-control	-	20 / 151	45 / 282	-
12	Parkin 2011	Nested case-control	-	-	44 / 233	-
13	Lewis 1996	Case-control	-	-	-	-
Design refers to the type and number of direct comparisons provided in a single study						
Studies with the same design provide direct comparisons of exactly the same generations or same individual oral contraceptives						

Table 8. Included publications with data on the 7 / 10 selected contraceptives and reference group non-use (continuation of Table 7)

Design	Study	Study design	Non-use	20 GSD	30 GSD	20 DSG	30 DSG	35 NRG	35 CPA	30 DRSP
			n event / n total							
1	van Hylckama Vlieg 2009	Case-control	421 / 1,523	14 / 32	119 / 186	58 / 85	289 / 397	9 / 13	125 / 187	19 / 33
2	Lidegaard 2011	Cohort	1,812 / 4,960,730	321 / 472,118	738 / 668,355	322 / 470,982	201 / 170,249	165 / 267,664	109 / 120,934	266 / 286,859
3	Parkin 2000	Case-control	9 / 95	-	5 / 10	4 / 9	3 / 8	-	2 / 3	-
4	Lidegaard 2002	Case-control	458 / 2,738	6 / 36	206 / 692	58 / 187	63 / 153	18 / 118	-	-
5	Bloemenkamp 1999	Case-control	83 / 511	-	5 / 9	6 / 7	22 / 51	-	-	-
6	Bloemenkamp 1995	Case-control	46 / 150	-	-	-	37 / 52	-	-	-
7	Farmer 2000	Cohort	-	-	63 / 143,581	18 / 37,584	65 / 152,524	15 / 40,440	16 / 25,709	-

Table 8. Included publications with data on the 7 / 10 selected contraceptives and reference group non-use (continuation of Table 7) (Continued)

8	Todd 1999	Cohort	-	-	21 / 41, 947	9 / 10,426	23 / 39, 679	-	-	-
9	Farmer 1996	Cohort	-	-	5 / 30,500	-	10 / 34, 600	-	-	-
10	Jick 2006	Nested case-control	-	-	-	-	87 / 315	124/635	-	-
11	Bird 2013	Cohort	-	-	-	-	-	-	-	151/ 96217
	Jick 2011	Nested case-control	-	-	-	-	-	-	-	121/434
12	Parkin 2011	Nested case-control	-	-	-	-	-	-	-	17/43
13	Lewis 1996	Case-control	-	-	-	15 / 51	64 / 174	19 / 50	-	-

Design refers to the type and number of direct comparisons provided in a single study

Design refers to the number of direct comparisons provided in a single study

Studies with the same design provide direct comparisons of exactly the same generations or same individual oral contraceptives

Studies with the same design provide direct comparisons of exactly the same generations or same individual oral contraceptives

Table 9. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part I

Comparisons	Study					
	van Hylckama Vlieg 2009	Lidegaard 2011	Parkin 2000	Lidegaard 2002	Bloemenkamp 1999	Bloemenkamp 1995
20LNG vs non-use	-	-	-	-	-	-
30LNG vs non-use	3.6 (2.9-4.6)	2.2 (1.7-2.8)	-	-	3.7 (1.9-7.2)	3.8 (1.7-8.4)

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Table 9. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part I (Continued)

50LNG vs non-use	-	3.5 (2.5-5.1)	-	5.3 (2.3-12.3)	-	-
20GSD vs non-use	-	3.5 (3.1-4.0)	-	2.0 (0.7-5.7)	-	-
30GSD vs non-use	5.6 (3.7-8.4)	4.2 (3.9-4.6)	-	3.5 (2.8-4.5)	5.2 (1.3-20.6)	-
20DSG vs non-use	-	3.3 (2.9-3.7)	-	4.8 (3.2-7.1)	24.7 (2.8-213.5)	-
30DSG vs non-use	7.3 (5.3-10.0)	4.2 (3.6-4.9)	-	5.4 (3.6-8.0)	4.9 (2.5-9.4)	8.7 (3.9-19.3)
35NRG vs non-use	5.9 (1.7-21.0)	2.6 (2.2-3.0)	-	1.7 (1.0-3.1)	-	-
35CPA vs non-use	6.8 (4.7-10.0)	4.1 (3.4-5.0)	17.6 (2.7-113.0)	3.3 (1.4-7.6)	-	-
30DRSP vs non-use	6.3 (2.9-13.7)	4.5 (3.9-5.1)	-	-	-	-
30LNG vs 20LNG	0.9 (0.3-2.5)	-	-	-	-	-
50LNG vs 20LNG	-	-	-	-	-	-
20GSD vs 20LNG	-	-	-	-	-	-
30GSD vs 20LNG	-	-	-	-	-	-
20DSG vs 20LNG	-	-	-	-	-	-
30DSG vs 20LNG	-	-	-	-	-	-
35NRG vs 20LNG	-	-	-	-	-	-
35CPA vs 20LNG	-	-	-	-	-	-
30DRSP vs 20LNG	-	-	-	-	-	-

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Table 9. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part I *(Continued)*

50LNG 30LNG	vs	2.2 (1.3-3.7)	-	-	-	-	-
20GSD 30LNG	vs	-	-	-	-	-	-
30GSD 30LNG	vs	-	-	-	-	-	-
20DSG 30LNG	vs	-	-	-	-	-	-
30DSG 30LNG	vs	-	-	-	-	-	-
35NRG 30LNG	vs	-	-	-	-	-	-
35CPA 30LNG	vs	-	-	-	-	-	-
30DRSP 30LNG	vs	-	-	-	-	-	-
20GSD 50LNG	vs	-	-	-	-	-	-
30GSD 50LNG	vs	-	-	-	-	-	-
20DSG 50LNG	vs	-	-	-	-	-	-
30DSG 50LNG	vs	-	-	-	-	-	-
35NRG 50LNG	vs	-	-	-	-	-	-
35CPA 50LNG	vs	-	-	-	-	-	-
30DRSP 50LNG	vs	-	-	-	-	-	-
30GSD 20GSD	vs	3.3 (1.4-7.1)	-	-	-	-	-
20DSG 20GSD	vs	-	-	-	-	-	-

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Table 9. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part I *(Continued)*

30DSG 20GSD	vs	-	-	-	-	-	-
35NRG 20GSD	vs	-	-	-	-	-	-
35CPA 20GSD	vs	-	-	-	-	-	-
30DRSP 20GSD	vs	-	-	-	-	-	-
20DSG 30GSD	vs	-	-	-	-	-	-
30DSG 30GSD	vs	-	-	-	-	-	-
35NRG 30GSD	vs	-	-	-	-	-	-
35CPA 30GSD	vs	-	-	-	-	-	-
30DRSP 30GSD	vs	-	-	-	-	-	-
30DSG 20DSG	vs	1.4 (0.8-2.5)	-	-	-	-	-
35NRG 20DSG	vs	-	-	-	-	-	-
35CPA 20DSG	vs	-	-	-	-	-	-
30DRSP 20DSG	vs	-	-	-	-	-	-
35NRG 30DSG	vs	-	-	-	-	-	-
35CPA 30DSG	vs	-	-	-	-	-	-
30DRSP 30DSG	vs	-	-	-	-	-	-
35CPA 35NRG	vs	-	-	-	-	-	-

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Table 9. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part I (Continued)

30DRSP 35NRG	vs	-	-	-	-	-	-
30DRSP 35CPA	vs	-	-	-	-	-	-

Table 10. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part II

Compar- isons	Study							
	Farmer 2000*	Todd 1999	Farmer 1996	Jick 2006	Bird 2013	Jick 2011	Parkin 2011	Lewis 1996
20LNG vs non-use	-	-	-	-	-	-	-	-
30LNG vs non-use	-	-	-	-	-	-	-	-
50LNG vs non-use	-	-	-	-	-	-	-	-
20GSD vs non-use	-	-	-	-	-	-	-	-
30GSD vs non-use	-	-	-	-	-	-	-	-
20DSG vs non-use	-	-	-	-	-	-	-	-
30DSG vs non-use	-	-	-	-	-	-	-	-
35NRG vs non-use	-	-	-	-	-	-	-	-
35CPA vs non-use	-	-	-	-	-	-	-	-
30DRSP vs non-use	-	-	-	-	-	-	-	-
30LNG vs 20LNG	-	-	-	-	-	-	-	-

Table 10. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part II *(Continued)*

50LNG 20LNG	vs	-	-	-	-	-	-	-	-
20GSD 20LNG	vs	-	-	-	-	-	-	-	-
30GSD 20LNG	vs	-	-	-	-	-	-	-	-
20DSG 20LNG	vs	-	-	-	-	-	-	-	-
30DSG 20LNG	vs	-	-	-	-	-	-	-	-
35NRG 20LNG	vs	-	-	-	-	-	-	-	-
35CPA 20LNG	vs	-	-	-	-	-	-	-	-
30DRSP 20LNG	vs	-	-	-	-	-	3.2 (1.8-5.5)	-	-
50LNG 30LNG	vs	-	-	-	-	-	-	-	-
20GSD 30LNG	vs	-	-	-	-	-	-	-	-
30GSD 30LNG	vs	1.3 (0.9-1.9)	-	-	-	-	-	-	-
20DSG 30LNG	vs	1.4 (0.8-2.4)	-	-	-	-	-	-	-
30DSG 30LNG	vs	1.3 (0.9-1.8)	-	1.5 (0.3-8.3)	1.7 (1.2-2.4)	-	-	-	-
35NRG 30LNG	vs	1.1 (0.6-2.0)	-	-	1.1 (0.8-1.5)	-	-	-	-
35CPA 30LNG	vs	1.8 (0.9-3.2)	-	-	-	-	-	-	-
30DRSP 30LNG	vs	-	-	-	-	1.8 (1.3-2.5)	2.2 (1.5-3.4)	3.3 (1.4-7.6)	-
20GSD 50LNG	vs	-	-	-	-	-	-	-	-

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Table 10. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part II *(Continued)*

30GSD 50LNG	vs	-	-	-	-	-	-	-	-
20DSG 50LNG	vs	-	-	-	-	-	-	-	-
30DSG 50LNG	vs	-	-	-	-	-	-	-	-
35NRG 50LNG	vs	-	-	-	-	-	-	-	-
35CPA 50LNG	vs	-	-	-	-	-	-	-	-
30DRSP 50LNG	vs	-	-	-	-	-	-	-	-
30GSD 20GSD	vs	-	-	-	-	-	-	-	-
20DSG 20GSD	vs	-	-	-	-	-	-	-	-
30DSG 20GSD	vs	-	-	-	-	-	-	-	-
35NRG 20GSD	vs	-	-	-	-	-	-	-	-
35CPA 20GSD	vs	-	-	-	-	-	-	-	-
30DRSP 20GSD	vs	-	-	-	-	-	-	-	-
20DSG 30GSD	vs	-	-	-	-	-	-	-	-
30DSG 30GSD	vs	-	-	1.2 (0.3-4.0)	-	-	-	-	-
35NRG 30GSD	vs	-	-	-	-	-	-	-	-
35CPA 30GSD	vs	-	-	-	-	-	-	-	-
30DRSP 30GSD	vs	-	-	-	-	-	-	-	-

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Table 10. Study specific adjusted risk estimates: per combined oral contraceptive in RR (95% CI) part II *(Continued)*

30DSG vs 20DSG	-	-	-	-	-	-	-	-	-
35NRG vs 20DSG	-	-	-	-	-	-	-	-	-
35CPA vs 20DSG	-	-	-	-	-	-	-	-	-
30DRSP vs 20DSG	-	-	-	-	-	-	-	-	-
35NRG vs 30DSG	-	-	-	-	-	-	-	-	-
35CPA vs 30DSG	-	-	-	-	-	-	-	-	-
30DRSP vs 30DSG	-	-	-	-	-	-	-	-	-
35CPA vs 35NRG	-	-	-	-	-	-	-	-	-
30DRSP vs 35NRG	-	-	-	-	-	-	-	-	-
30DRSP vs 35CPA	-	-	-	-	-	-	-	-	-

Table 11. Results of the network meta-analysis per combined oral contraceptive pill

Non-use											
(reference group)	20 LNG	30 LNG	50 LNG	20 GSD	30 GSD	20 DSG	30 DSG	35 NRG	35 CPA	30 DRSP	
Non-use	1										
20 LNG	2.2 (1.3-3.6)	1	0.9 (0.6-1.4)	0.4 (0.2-0.8)	1.0 (0.6-1.8)	0.6 (0.4-1.0)	0.7 (0.4-1.1)	0.5 (0.3-0.8)	0.9 (0.5-1.5)	0.6 (0.3-1.0)	0.6 (0.4-0.9)
30 LNG	2.4 (1.8-3.2)	1.1 (0.7-1.7)	1	0.5 (0.3-0.7)	1.1 (0.8-1.7)	0.7 (0.5-0.9)	0.7 (0.5-1.0)	0.6 (0.4-0.7)	1.0 (0.7-1.4)	0.6 (0.4-0.9)	0.6 (0.5-0.8)

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Table 11. Results of the network meta-analysis per combined oral contraceptive pill *(Continued)*

50 LNG	5.2 (3.4-7.9)	2.3 (1.3-4.2)	2.1 (1.4-3.2)	1	2.4 (1.5-4.0)	1.4 (0.9-2.1)	1.5 (1.0-2.4)	1.2 (0.8-1.8)	2.2 (1.4-3.3)	1.3 (0.8-2.1)	1.3 (0.8-2.1)
20 GSD	2.2 (1.4-3.2)	1.0 (0.5-1.7)	0.9 (0.6-1.3)	0.4 (0.3-0.7)	1	0.6 (0.4-0.9)	0.6 (0.4-1.0)	0.5 (0.3-0.7)	0.9 (0.6-1.4)	0.6 (0.4-0.8)	0.6 (0.4-0.9)
30 GSD	3.7 (2.8-4.9)	1.7 (1.0-2.7)	1.5 (1.2-2.0)	0.7 (0.5-1.1)	1.7 (1.1-2.6)	1	1.1 (0.8-1.5)	0.9 (0.7-1.1)	1.5 (1.1-2.1)	1.0 (0.7-1.4)	1.0 (0.7-1.3)
20 DSG	3.4 (2.5-4.6)	1.5 (0.9-2.6)	1.4 (1.0-1.9)	0.7 (0.4-1.0)	1.6 (1.0-2.4)	0.9 (0.7-1.2)	1	0.8 (0.6-1.1)	1.4 (1.0-2.0)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
30 DSG	4.3 (3.3-5.6)	1.9 (1.2-3.1)	1.8 (1.4-2.2)	0.8 (0.5-1.2)	2.0 (1.3-2.9)	1.2 (0.9-1.5)	1.3 (0.9-1.7)	1	1.8 (1.3-2.4)	1.1 (0.8-1.6)	1.1 (0.8-1.5)
35 NRG	2.4 (1.7-3.3)	1.1 (0.7-1.8)	1.0 (0.7-1.3)	0.5 (0.3-0.7)	1.1 (0.7-1.7)	0.7 (0.5-0.9)	0.7 (0.5-1.0)	0.6 (0.4-0.8)	1	0.6 (0.4-0.9)	0.6 (0.4-0.9)
35 CPA	3.9 (2.7-5.5)	1.7 (1.0-3.0)	1.6 (1.1-2.2)	0.7 (0.5-1.2)	1.8 (1.1-2.8)	1.0 (0.7-1.5)	1.1 (0.8-1.6)	0.9 (0.6-1.3)	1.6 (1.1-2.3)	1	1.0 (0.7-1.5)
30 DRSP	3.9 (2.7-5.5)	1.7 (1.1-2.7)	1.6 (1.2-2.1)	0.7 (0.5-1.2)	1.8 (1.2-2.8)	1.1 (0.7-1.5)	1.1 (0.8-1.6)	0.9 (0.7-1.3)	1.6 (1.1-2.3)	1.0 (0.7-1.5)	1

Table 12. Results of sensitivity analyses

Source of bias and No of studies							
Generation of progestogen	Industry (n=8)	Non-industry (n=9)	Cohort (n=8)	study	Case-control (n=15)	Objectively confirmed venous thrombosis (n=5)	Subjectively confirmed venous thrombosis (n=11)
Non-use	1	1	1		1	1	1
1st	2.6 (0.9-7.4)	3.3 (2.4-4.6)	2.0 (0.4-10.5)		3.3 (2.3-4.7)	4.5 (3.2-6.5)	2.6 (1.3-5.3)
2nd	2.1 (1.0-4.8)	3.1 (2.5-3.8)	1.7 (0.4-8.0)		2.9 (2.3-3.7)	3.3 (2.8-4.0)	2.5 (1.4-4.5)
3rd	1.9 (0.8-4.2)	5.2 (4.2-6.5)	2.0 (0.5-8.6)		4.2 (3.3-5.3)	6.2 (5.2-7.4)	3.0 (1.7-5.4)
Data are relative risk (95% confidence interval) of venous thrombosis							

APPENDICES

Appendix I. Search strategy for the review

Cochrane Database of Systematic Reviews (<http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME>)

("oral contraceptives" OR "oral contraceptive" OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon*) AND ("Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate" OR "estradiol valerate")) AND ("deep vein thrombosis" OR "deep venous thrombosis" OR "Venous Thrombosis" OR "Vein Thrombosis" OR "Vein Thrombosis" OR Thrombophlebitis OR "pulmonary embolism" OR "venous thromboembolism" OR "venous thromboembolic disorder" OR "venous thromboembolic disease" OR "venous thrombotic") AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

PubMed (<http://www.ncbi.nlm.nih.gov/entrez/>)

("Contraceptives, Oral"[MeSH] OR "Contraceptives, Oral"[Pharmacological Action] OR "oral contraceptives" OR "oral contraceptive" OR "Contraceptives, Oral, Combined"[MeSH] OR "combined oral contraceptives" OR "combined oral contraceptive" OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon* OR oestrogen*[ti] OR estrogen[ti]) AND ("Ethinyl Estradiol"[MeSH] OR "Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate"[Supplementary Concept] OR "estradiol valerate" OR progestogen*[ti])) AND ("deep vein thrombosis"[ti] OR "deep venous thrombosis"[ti] OR "Venous Thrombosis"[ti] OR "Vein Thrombosis"[ti] OR "Venous Thrombosis"[MeSH:noexp] OR "Thrombophlebitis"[MeSH] OR "Upper Extremity Deep Vein Thrombosis"[MeSH] OR Thrombophlebitis[ti] OR "pulmonary embolism"[ti] OR "pulmonary embolism"[MeSH] OR "venous thromboembolism"[ti] OR "Venous Thromboembolism"[MeSH] OR "venous thromboembolic disorders"[ti] OR (venous[ti] AND thromboembolic[ti] AND disorder[ti]) OR "venous thromboembolic diseases"[ti] OR "venous thromboembolic disease"[ti] OR "venous thrombotic"[ti] OR ("Thromboembolism"[MeSH: noexp] AND (venous[tiab] OR vein[tiab] OR veins[tiab])) AND (risk OR risks OR risk factor OR risk factors) AND (women OR woman OR woman* OR women* OR girl OR girls OR female) NOT (animals NOT (human AND animals)))

EMBASE (<http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=N&PAGE=main&D=emez>)

(exp oral contraceptive agent/ OR "oral contraceptives".mp OR "oral contraceptive".mp OR "combined oral contraceptives".mp OR "combined oral contraceptive".mp OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon*).mp OR oestrogen*.ti OR estrogen.ti) AND ((("Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate" OR "estradiol valerate").mp OR progestogen*.ti))) AND ((("deep vein thrombosis" OR "deep venous thrombosis" OR "Venous Thrombosis" OR "Vein Thrombosis").ti OR exp deep vein thrombosis/ OR Vein Thrombosis/ OR Thrombophlebitis/ OR Thrombophlebitis.ti OR "pulmonary embolism".ti OR exp lung embolism/ OR "venous thromboembolism".ti OR exp Venous Thromboembolism/ OR "venous thromboembolic disorder".ti OR "venous thromboembolic disease".ti OR "venous thrombotic".ti) AND (exp risk/ OR risk*.mp OR exp risk factor/) AND ((women OR woman OR woman* OR women* OR girl OR girls OR female).mp OR exp female/) AND (exp human/ OR human.ti OR patient.ti OR patients.ti))

CINAHL (<http://search.ebscohost.com/login.aspx?authtype=ip.uid&profile=lumc&defaultdb=cin20>)

TITLE/ABSTRACT/KEYWORD

(oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*)

AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate*)) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

Web of Science (<http://isiknowledge.com/wos>)

TS=(“oral contraceptives” OR “oral contraceptive” OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR “ethynodiol diacetate” OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR “medroxyprogesterone acetate” OR “chlormadinone acetate” OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR “Cyproterone acetate” OR Drospirenone OR Drospirenon*) AND (“Ethinyl Estradiol” OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR “estradiol valerate” OR “estradiol valerate”*)) AND TI=(“deep vein thrombosis” OR “deep venous thrombosis” OR “Venous Thrombosis” OR “Vein Thrombosis” OR “Thrombophlebitis” OR “pulmonary embolism” OR “venous thromboembolism” OR “venous thromboembolic disorder*” OR “venous thromboembolic disease*” OR “venous thrombotic”) AND TS=risk* AND TS=(women OR woman OR woman* OR women* OR girl OR girls OR female)

Academic Search Premier (<http://search.ebscohost.com/login.aspx?authtype=ip.uid&profile=lumc&defaultdb=aph>)

title/su/kw/ab

(oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*)) AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate*)) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

ScienceDirect

(http://www.sciencedirect.com/science?_ob=MiamiSearchURL&_method=requestForm&_temp=all'boolSearch.tmpl&_acct=C000026638&_version=1&_urlVersion=1&_userid=530453&md5=d44bd9fa9076bb9b258a588b309be1e3)

TITLE((oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestim* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*)) AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate*)) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female))

CONTRIBUTIONS OF AUTHORS

M de Bastos, BH Stegeman, and OM Dekkers drafted and edited the protocol. A van Hylckama Vlieg, FR Rosendaal, and FM Helmerhorst advised on the protocol and provided clinical and technical expertise for the systematic review. T Stijnen provided statistical expertise. BHS, MdB, FMH, and OMD developed the study design. BHS and MdB independently selected the publications and extracted data. BHS, TS, and OMD performed the statistical analysis. All authors interpreted the data and critically reviewed drafts of the manuscript.

DECLARATIONS OF INTEREST

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- CAPES-NUFFIC, Brazil.

MdB is a grant holder from CAPES-NUFFIC, Brazil

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were able to carry out most of the planned activities of the protocol. The missing evaluations concerned absolute risk evaluation, specific sensitivity analyses and graphical representation of the network and the results. Absolute VT risk of individual COC estimates or loss of follow-up estimates were not usually reported in the included studies. Due to the small number of included studies and the non-standardized data reporting in the included studies, some sensitivity analyses were not possible (e.g., sensitivity analysis on calendar time). Due to the complexity of the network (10 combined oral contraceptives and a non-use group resulting in 55 possible comparisons), a clear representation of the network was not possible nor a forest plot.

INDEX TERMS

Medical Subject Headings (MeSH)

Androstenes [adverse effects]; Contraceptives, Oral, Combined [*adverse effects]; Cyproterone [adverse effects]; Desogestrel [adverse effects]; Ethinyl Estradiol [adverse effects]; Levonorgestrel [adverse effects]; Norpregnones [adverse effects]; Pulmonary Embolism [*chemically induced]; Randomized Controlled Trials as Topic; Venous Thrombosis [*chemically induced]

MeSH check words

Female; Humans